A-0166

Icotinib & Phase IV ISAFE trial

Safety and Efficacy Results of an Open-label, Multicenter Safety-monitoring Study in Non-small Cell Lung Cancer Patients (NSCLC)

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ABSTRACT

Background: Icotinib is a highly selective and potent epidermal growth factor receptor (EGFR) tyrosine-kinase inhibitor. In a phase III clinical trial (ICOGEN), icotinib was shown to be non-inferior to another EGFR-TKI, gefitinib, in terms of progression-free survival (4.6 [3.5-6.3] months vs. 3.4 [2.3-3.8] months; p=0.13). Icotinib was approved by the CFDA in June 2011 for use as second- or third-line therapy for advanced non-small cell lung cancer (NSCLC) patients. Upon approval of icotinib, a phase IV study (ISAFE) was initiated in China to complete further safety and efficacy assessment of the drug.

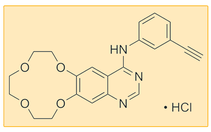
Aims: To confirm the safety and efficacy of icotinib in the clinical setting.

Methods: The trial was a single-arm, open-label, phase IV study, conducted in 480 hospitals in China. Advanced NSCLC patients who were suitable for treatment, were administered oral icotinib (125 mg, TID) until disease progression or intolerable toxicity occurred. Objectives included safety assessment, tumor response, overall response rate (ORR) and disease control rate (DCR).

Results: 6,087 patients were registered in the study, 5,548 were evaluable for safety and tumor response with a median age of 63 years (range: 21-95 years). Baseline characteristics (%): male/female 50.8/49.2; non-smoker/ex- or current smoker/no data 67.2/32.7/0.1; adenocarcinoma/non-adenocarcinoma/other 78.6/15.4/6.0; stage IIIB/IV/other 7.4/90.2/2.4. The overall incidence of drug-related adverse events was 31.5%. The most common AEs were rash (17.4%) and diarrhea (8.5%), and 3 patients experienced interstitial lung disease associated with icotinib. The ORR was 30.0% and the DCR was 80.6%.

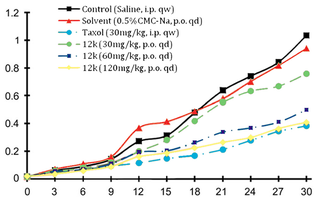
Conclusion: Through both the ICOGEN trial and phase IV safety study (ISAFE), icotinib has been shown to be both safe and effective for the treatment of patients with advanced NSCLC. Since drug approval in 2011, more than 40,000 NSCLC patients have been treated with icotinib in China. Icotinib is currently under worldwide development, with plans to expand access to the whole of Asia in the near future.

INTRODUCTION



- EGFR is a transmembrane protein that is frequently activated in many human cancers and leads to increased proliferation and survival of cancer cells.
- Common EGFR mutations are short, in-frame deletions in exon 19 (del19) and specific point mutations in exon 21 (L858R).
- Mutation of EGFR is found to be an oncogenic driver in many human solid tumors, including breast, ovarian, non-small cell lung cancer (NSCLC), colorectal, and head and neck cancers.
- Icotinib (BPI-2009H) is a highly selective and specific EGFR inhibitor (IC50 EGFR = 2 nM) belonging to the aminoquinazoline class of tyrosine kinase inhibitors.
- In 2009, icotinib underwent a randomized, double-blind phase 3 clinical trial (ICOGEN) where it was tested head-to-head with another EGFR-TKI, gefinitib.
- The results of the ICOGEN trial showed that icotinib was non-inferior to gefitinib in terms of progression free survival and overall survival.
- Icotinib showed a slight improvement over gefitinib in terms of overall toxicity and reported adverse events (61% vs. 70%), however it was not deemed statistically significant.
- Icotinib gained marketing approval from the CFDA on June 7, 2011. Upon market approval, icotinib began a phase IV, safety monitoring study (ISAFE) to determine safety and efficacy in a wider population.

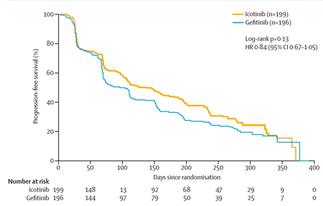
IN VIVO TUMOR MODEL



Pharmacokinetic properties of the selected compound **12k**

F (%) (rat)	52
C_{max} (po)	6.12 μg/mL
AUC (po)	49.4 μg/mL
$T_{1/2}$ (po)	2.8 h
Cl	21 mL/min/kg
Vss	3.9 L/kg
MRT	6.9 h

PROGRESSION-FREE SURVIVAL



PHASE IV (ISAFE) DATA

METHODS

- Single-arm, open-label, phase IV study.
- Conducted in 480 hospitals in China.
- Advanced NSCLC patients administered oral icotinib (125mg, TID) until disease progression or intolerable toxicity.

STUDY OBJECTIVES

Primary Objectives

- Assess safety of icotinib, noting all newly reported and severse adverse events

Secondary Objectives

- Tumor response, measured in terms of objective response rate (ORR) and disease control rate (DCR)
- Safety and efficacy of icotinib in elderly patients (≥ 70 years)

BASELINE CHARACTERISTICS

Characteristics		N (%)
Age	< 70	4,325 (71.1%)
	≥ 70	1,722 (28.3%)
	Unknown	40 (0.7%)
Gender	Male	3,092 (50.8%)
	Female	2,995 (49.2%)
Pathology	Adenocarcinoma	4,783 (78.6%)
	Non-Adenocarcinoma	935 (15.4%)
	Other	369 (6.1%)
Disease Stage	IIIB	452 (7.4%)
	IV	5,488 (90.2%)
	Other	139 (2.3%)
Smoking Status	Unknown	8 (0.1%)
	Smokers	675 (11.1%)
	Non-smokers	4,093 (67.2%)
	Ex-smokers	1,319 (21.7%)
Previous Chemotherapy regimens	0*	1,026 (16.9%)
	1	2,829 (46.5%)
	≥2	2,114 (34.7%)
	Other**	116 (1.91%)

* Patients deemed intolerant to chemotherapy received icotinib as first-line treatment
** Includes adjuvant therapy, maintenance therapy and unknown.

EGFR STATUS & TUMOR RESPONSE

EGFR gene status**		CR	PR	SD	PD/Death	ORR	DCR	Total
Mutated	19del	5	159 (49.8%)	141	9/5	51.4%	95.6%	319
	L858R	7	147 (45.4%)	138	26/6	47.5%	90.1%	324
	Other	0	9 (40.9%)	8	5/0	40.9%	77.3%	22
Wild Type		3	35 (16.4%)	124	42/10	17.8%	75.7%	214
Total		15	350 (39.8%)	411	103	41.5%	88.3%	879

** only 989/6,087 patients underwent EGFR mutation testing

PATIENT ENROLLMENT

Patients
- Advanced NSCLC
- Any number of prior therapies
- Age 21 - 95 years
- EGFR status unknown

Enrollment: August 2011 - August 2012
6,087 patients accrued
Data cut-off point: October 2012

Safety and efficacy population: 5,549
- 538 patients excluded due to:
  - No available CRF data: 360
  - Did not complete at least 1 course of treatment: 109
  - Other: 69

Elderly subgroup (n = 1,571)

EGFR mutation subgroup (n = 738)

ADVERSE REACTIONS

	Overall population/Elder patients				
Adverse reactions	**Grade I**	**Grade II**	**Grade III**	**Unknown**	**Total**
Rash	816/218	140/44	8/1	0/0	964/263
Diarrhea	399/106	50/13	6/2	14/6	469/127
Elevated ALT	22/4	6/1	3/0	1/1	32/6
Elevated AST	9/1	5/2	0/0	0/0	14/3
ILD	0/0	0/0	3/2	0/0	3/2
Other	56/16	22/5	8/7	178/51	264/79
Total	**1,302/345**	**223/65**	**28/12**	**193/58**	**1,748/480**
Percentage (%)	**23.5/22.0**	**4.0/4.1**	**0.5/0.8**	**3.5/3.7**	**31.5/30.6**

CLINICAL CHARACTERISTICS &TUMOR RESPONSE

		N	ORR	DCR
Gender	Male	2,792	24.6%	76.4%
	Female	2,757	35.4%	84.8%
Smoking Status	Non-smoker	3,759	33.6%	83.9%
	Smoker	602	22.8%	71.6%
Pathology type	Non-adeno	872	16.3%	67.5%
	Adeno	4,354	33.0%	83.6%

INVESTIGATORS & SITES

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CONCLUSIONS

- Icotinib is a safe and effective EGFR tyrosine kinase inhibitor for the treatment of NSCLC.
- The phase IV, ISAFE study showed icotinib to have acceptable safety and favorably tolerability in a broad NSCLC patient population, with low adverse events rate of 31.5%.
- In an EGFR mutation positive population, icotinib showed an excellent ORR of 49.2% and a disease control rate (DCR) of 92.3%.
- EGFR mutation positive patients who received first-line icotinib showed an ORR of 56.3%.

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FURTHER INFORMATION

Global Development

- January 2014 - the United States FDA gave icotinib a "May Proceed" letter to begin US clinical trials.
- US Phase I clinical trial enrollment to begin Q1 2015
- For more information
  - Visit http://www.betapharma.com/products/icotinib-hydrochloride
  - E-mail: clinical.research@betapharma.com

Acknowledgments

- These studies were sponsored by Zhejiang Betta Pharmaceuticals Co.,Ltd.
- This poster was sponsored and presented by Beta Pharma, Inc. USA.

2014 IASLC Asia Pacific Lung Cancer Conference (APLCC) celebrating 10th year's anniversary

IASLC International Association for the Study of Lung Cancer